REMARKS

Claim 1-20 were examined in the present Office Action.

The Office Action has been carefully studied. Applicants have amended claim 1 extensively, as well as introducing corresponding minor amendments into other claims (primarily amending "host cell" to "cell" for simplicity). Claim 5 has been cancelled and the dependency of claim 6r altered accordingly. New claims 21-24 have been added.

None of the amendments or new claims introduce new matter. Support for the amendment of claim 1 can be found at least at page 7, lines 6-11 (as well as in original claim 5). New claims 21-24 are supported in the paragraph bridging pages 7 and 8.

Entry of these amendments and consideration of the Remarks below are respectfully requested. Applicants believe that the claims are now in condition for allowance.

I. Formalities

A. Title

The title of the invention is allegedly not descriptive. The Office requires a new title that is clearly indicative of the invention to which the claims are directed. The title has been amended above.

B. Sequence Listing

This application is said not to be in compliance with 37 CFR §§ 1.821 through 1.825 for reasons. set forth in the enclosed SEQUENCE LISTING ERROR REPORT dated 02/17/2005. The Office has required appropriate correction. Applicants submitted a corrected Sequence Listing and Statement of Identity on May 2, 2007, after the date of mailing of this Office Action. Thus, Applicants believe that no further action is needed on this point.

C. Information Disclosure Statement

The Information Disclosure Statement (IDS) filed .07/07/2004 **fails to comply** with 37CFR 1.98(a)(2). The undersigned learned from a telephone call to the Examiner on September 10, 2007, that the references cited in the above IDS were not received by the Office, and the Examiner requested copies be submitted herewith which he would consider upon their entry into the record.

Applicants submit the following references *(and rely on the original "SubstitutePTO-1449"):*

(1) PCT Patent Publication WO 96/24667;

(2) GenBank Record AJ249909;

(3) GenBank Record AJ249910;

(4) Zaldivar, J. *et al., Applied Microbiol Biotechnol. 56 (1-2):*17-34 (2001 July) ("Fuel ethanol production from lignocellulose: A challenge for metabolic engineering and process integration"); and

(5) Teunissen, M.J. *et al.*; *J Gen Microbiol 138 (8)*:1657-64 (1992) ("Production of cellulolytic and xylanolytic enzymes during growth of the anaerobic fungus piromyces-sp on different substrates").

II. Rejections for Lack of Enablement under 35 U.S.C. §112, 1st Paragraph

Claims 1-11 were rejected for lack of enablement. The specification was said to enable claims to an isolated eukaryotic host cell transformed with a polynucleotide encoding a xylose isomerase *consisting of* the amino acid sequence SEQ ID NO: 1. However the Office contends that the specification does not enable any other embodiment recited in the claims.

Claims 12-20 were rejected as their nature and scope were said to encompass "any process" for producing ethanol (or a series of other products) using "any eukaryotic host cell" transformed "with any nucleic acid construct comprising any nucleotide sequence encoding any xylose isomerase comprising an amino acid sequence that is at least 70% identical to SEQ ID NO: 1."

The Office Action focuses on four aspects of the claims in its analysis.

(a) the xylose isomerase (xylose isomerase) used having at least 70% identity with the xylose isomerase of *Piromyces sp.* E2 (SEQ ID NO:1);

(b) the genetic modifications introduced in the eukaryotic strain (claims 7-11 and 16);

(c) the types of cell claimed (ranging from *in vitro* cell culture up to multicellular organisms);

(d) the product produced (claims 12-20);

Applicants' Response

To begin, Applicants note that they have amended claim 1 in several ways; the significance of these amendments is discussed below. First "A eukaryotic host cell …" have been limited and is now claimed as "A cultured eukaryotic cell…". Next, the ending of the claim that was directed to the transformed cell's ability to "grow on xylulose as a carbon source" has been amended to recited that, as a result of the transformation, the cell has "the ability to directly isomerize xylose to xylulose." Support for the latter amendment can be found, inter alia, at page 7, lines 6-11.

A. Scope of Xylose Isomerase Sequences

As indicated above, the Office takes that position that the application only enables claims limited to the specific xylose isomerase isolated from *Piromyces* sp E2 (*i.e.*, the protein with SEQ ID NO:1). Applicants disagree and contend that this approach to the question of support constitutes an unfair restriction of claim scope that would not be commensurate with the inventors' contribution to the art. Moreover, it also appears to overlook support for a broader range of xylose isomerases that is present in the application.

The specification discloses at page 8 (lines 18-23) that the most preferred nucleotide sequences encoding a xylose isomerase for use in the present invention are those from anaerobic fungi in view of the increased likelihood of their being expressed in eukaryotic host cells. The specific *Piromyces* sequence (SEQ ID NO:1) is but one example from such fungi. Several specific examples of related anaerobic fungi are provided at page 8 (lines 22-23). The skilled artisan could readily use SEQ ID NO:1 as a hybridization-probe or as a foundation for designing degenerate PCR primers to related sequences (falling within the scope of the claim's requirement of 70% sequence identity) from the other anaerobic fungi. None of this would require undue experimentation.

In addition, Applicants wish to bring to the Examiner's attention later filed patent publications WO04/99381 and WO06/009434, the latter of which includes common inventors. These documents disclose another xylose isomerase having more than 70% identity with SEQ ID NO:1. This additional xylose isomerase also confers on transformed eukaryotic cells the ability to convert xylose directly to xylulose. One such xylose isomerase originates from plants (in WO04/99831), and more importantly, from *Bacteroides thetaiotaomicron* and has 83% identity with SEQ ID NO:1 (WO06/009434). Xylose isomerase from the anaerobic gut fungi *Cyllamyces aberensis* shares 97% sequence identity with SEQ ID NO:1 (WO04/99831).

Given the common general knowledge in the art, the skilled artisan has every reason to expect that xylose isomerases that have at least 70% sequence identity to the *Piromyces* enzyme (SEQ ID NO:1) will confer on a eukaryotic host the ability to convert xylose directly to xylulose as is now claimed. It goes without saying that the embodiments claimed in new claims 21-23, which have even higher sequence identity will have the same claimed property. The above post-filing evidence is yet further evidence supporting the disclosure of the present application and serves to rebut the Office's position

B. Genetic Modifications

This basis for rejection was directed to claims 7-11 and dependent process claims 16, 17 and 20, Applicants respectfully submit that the specification contains enabling guidance (page 10, line 16 through page 11, line 7). The application exemplifies several preferred genes that could be overexpressed or inactivated to obtain the cell having the desired phenotype. In light of this, Applicants strongly disagree with the position that, as of the priority date of this application, the acts of selecting a gene such as those discussed in the application followed by its modification, *e.g.*, expression or inactivation, in a given eukaryotic host strain to achieve the recited phenotypic characteristics, amounts to undue experimentation. Rather it would be nothing more than routine experimentation. Applicants position is further supported by the teachings of two references cited in this Office Action for different reasons (see prior art rejections discussed below)

Thus, Applicants believe that it would be proper, with respect to points A and B, above, to withdraw the rejection for lack of enablement.

C. Types of Cells

This ground for rejection seems to be based on the Office's view that the claims read on "host cells within a multicellular organism" (*i.e.*, *in vivo*). It was evident to the Examiner that the specification disclosed (and that the claims enable) the use of cells in culture. Claim 1, and thereby, all the dependent claims have been amended to recited "a cultured eukaryotic cell..." In view of this amendment, this basis for the enablement rejection may properly be withdrawn.

D. Products

This ground for rejection focuses on claim 12-20 and concerns lack of enablement of the product produced by the claimed process. Most of the points raised by the Office Action in support of this position are the same points discussed above in the context of claims to transformed cells. Applicants reiterate their reasoning above as to why claims that here are directed to a process in which

(i) the host cell is transformed with the indicated xylose isomerase-encoding DNA

(ii) the encoded xylose isomerase has an amino acid sequence which is at least 70% identical to SEQ ID NO: 1,

are adequately enabled by the specification.

Specifically regarding the process claims, Applicants discern only one additional point: the Office appears to be taking the position that the specification does not adequately enable the

use of the cells "in any process for producing ethanol, lactic acid, acetic acid, succinic acid, any amino acid, 1,3-propanediol, ethylene, glycerol, any β-lactam, or cephalosporin."

The Office relies on a reference by van Maris *et al., 2006,* (*Antonie Van Leeuwenhoek* 90:391-418 (Epub 2006 Oct 11) to describe the state of the art. The Action states that the art is notable for:

> lack of success of heterologous expression of xylose isomerase in yeast for the production of ethanol due to improper protein folding, posttranslational modifications, disulfide-bridge formation, and the internal pH of yeast.

(referring to entire publication, especially pgs. 400-401).

Indeed, the present invention represents an unexpected step forward in technology because it provides, for the first time the ability to transform the metabolic property of yeast/fungal cells which normally lack, or have a very weak, ability to convert xylose to xylulose and more typically accomplish this via a two-step rather than a direct one step catalysis. Indeed, as claimed in claim 1, the present invention enables, and focuses on, such "direct" xylose-xylulose conversion. Applicants contend that the failed attempts in the prior art to achieve what they have accomplished (and taught in the present specification) **is not evidence for lack of enablement** of the production of ethanol and the other listed products as claimed using the cells described in claim 1. Of course this new knowledge contributed by Applicants is coupled with what is generally known in the art with respect to the fermentation processes needed to produce the indicated products once the inventive concept (and the ability to carry it out) have been placed in the hands of the public. Indeed, Applicants have done so by their creation of eukaryotic cultured cells that can now carry out a single step conversion of xylose to xylulose, a direct conversion that has been desired and sought by others for years (see, for example, WO 96/24667)

The following several points are directed to the present "product-focused" rejection for lack of enablement.

(1) It is not immediately evident to Applicants what the Examiner means by "any process". Claim 12 recites a process that is nothing more than fermentation of a xylose-containing medium with the transformed cells to generate ethanol. Dependent claims 13-15 add additional limitations that do not appear to have any bearing on the rejection. Surely the Office cannot be concluding that the fermentation *as a process* is not enabled, once the key (novel) element is provided by Applicants.

(2) Claim 16 is "parallel" to claim 12 but directed to a group of other fermentation products. It does not appear to Applicants that the rejection of claim 16 is related *per se* to this list of products.

In view of (1) and (2) above, Applicants conclude that the basis for rejection of the process claims is in fact indistinguishable from the basis for rejection of the claims to transformed cells. Given that, Applicants remarks above regarding claim 1 *et seq.* should apply equally and fully to this aspect of the rejection.

(3) The Office Action further states that the specification does not provide guidance, working examples, or prediction for making the recited "genetic modifications" of claim **16** (along with host cells claims 7-11).

> *Furthermore, the specification does not provide guidance, working examples, or prediction for making the recited genetic modifications recited in claims 7-11 and* ***16.***
>
> **(Applicants believe the examiner intended claim 20, not 16, above).**

In any case, the discussion above refuting the rejection focused on the transformed cell claims applies equally to process claims 16, 17 and 20 .

Thus, Applicants request that the Office withdraw the rejection of claims 12-20 on the basis of the is § 112, first paragraph, for lack of enablement.

III. Rejections for Lack of Adequate Written Description under 35 US.C.§112, 1st Paragraph

The Office characterized the claims as being drawn to

(a) a ***genus*** of eukaryotic host cells transformed with ***any*** nucleic acid construct comprising ***any*** nucleotide sequence encoding **any** xylose isomerase comprising an amino acid sequences that is at least 70% identical to ·SEQ ID NO:1

(b) **a** genus of **processes for producing** ethanol, lactic acid, acetic acid, succinic acid, any amino acid, 1,3-propanediol, ethylene, glycerol, any β-lactam, or cephalosporin using the above **genus** of eukaryotic host cells.

The Office contends that the scope of the genus includes many members with widely differing structural, chemical, and physiochemical properties. including widely differing amino acid/nucleotide sequences and biological functions for the protein/enzymes in the recited biosynthetic path ways. Furthermore, each genus is highly variable because a significant number of structural and biological differences between genus members exist.

The Action indicates that, under MPEP§ 2163, a claimed genus will satisfy the written description requirement through sufficient description of a "**representative number of species**" by actual reduction to practice, reduction to drawings, by disclosure of relevant, identifying structure/physical/ chemical properties, by disclosure of functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of the foregoing characteristics, sufficient to show possession of the claimed genus. The Action cites the Federal Circuit decision *Regents of Univ. of Cal. v. Eli Lilly & Co.*,119 F.3d at 1568, 43 USPQ2d at 1406), (hereinafter "*Lilly*"). The Office further notes that according to MPEP § 2163, when there is substantial variation within the genus, Applicant must describe a sufficient variety of species to reflect such variation.

In its analysis of the present case, the Office concluded that the specification discloses only an isolated polynucleotide from *Piromyces* sp. E2 (ATCC 76762) encoding a xylose isomerase that consists of SEQ ID NO:1, yeast expression vectors containing this isolated polynucleotide, yeast cells transformed with this expression vectors, and the growth of these transformed yeast cells on xylose (citing Examples 1-4). The Office further asserts that the specification **fails to disclose additional eukaryotic host cells that would be encompassed by the claims**, and which, according to the Office, are widely variant in their physiological characteristics, functions, and/or structures.

The Office Action also states that the specification does not describe production of ethanol and the other listed products using the above yeast cells transformed with these expression vectors and does not provide a written description of the genetic modifications recited in claims 7-11 and 16 (Applicants believe the examiner meant claim 20 here, not claim 16.).

The Office Action cited the following from the *Lilly* decision,

> Written description of an invention involving a chemical genus like a description of a chemical species, 'requires a precise. definitions, such as the structure, formula [or] chemical name,' of the claimed subject matter sufficient to-distinguish it from other materials.

Lilly, quoting *Fiers v Revel, 984 F.2d* 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original).

The Office Action states that, based on *Lilly*,

> [t]o fully describe the genus of genetic materials, which is a chemical compound, applicants must **fully**-describe at least **one species** of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules…

(Office Action at page 6; emphasis added). On this basis the Office concluded that the instant claims are not adequately described.

Applicants' Response

The legal basis for the Written Description requirement was summarized by the Court of Customs and Patent Appeals, forerunner of the Federal Circuit, in *In re Wertheim*, 541 F.2d 257, 191 USPQ 90,96 (C.C.P.A. 1976)

> The function of the description requirement is to ensure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; how the specification accomplishes this is not material. *In re Smith*...178 USPQ 620 (CCPA 1973),....It is not necessary that the application describe the claim limitations exactly, *In re Lukach* [169 USPQ 795 (1971)], but only so clearly that persons of ordinary skill in the art will recognize from the disclosure that appellants invented processes including those limitations. *In re Smythe*... 178 USPQ 279,284 (CCPA 1973).

As the Federal Circuit Court of Appeals has explained more recently,

> ...[t]he "written description" requirement implements the principle that a patent must describe the technology that is sought to be patented; the requirement serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed.

Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1366 (Fed. Cir. 2006) (quoting *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir .2005)); *accord Monsanto Co. v. Scruggs*, 459 F.3d 1328 (Fed. Cir. 2006). The 'written description' requirement serves a teaching function, as a '*quid pro quo*' in which "the public is given 'meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time." *University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 922 (Fed. Cir.) (quoting *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d 956, 970 (Fed. Cir. 2002)), *cert. denied*, 543 U.S. 1015 (2004). "[T]he purpose of the written description requirement is [also] to 'ensure that the scope of the right to exclude, as set forth in the claims, does not overreach the scope of the inventor's contribution to the field of art as described in the patent specification.'" *Id.* at 920 (quoting *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991)). The requirement is met if "'the patent disclosure provides ample support for the breadth of the term [and] does not "unambiguously limit[ ]" the meaning of [the term]' to the narrower embodiment." *Cordis Corp.*, 339 F.3d at 1365 (quoting *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 993 (Fed. Cir. 1999), in turn quoting *Gentry Gallery, Inc.*, 134 F.3d at 1480). Thus, "the patent's 'disclosure must allow one skilled in the art "to visualize or recognize the identity of" the subject matter purportedly described.'" *Koito Mfg. Co., Ltd. v. Turn- Key-Tech, L.L.C.*, 381 F.3d 1142, 1154 (Fed. Cir. 2004) (quoting *Enzo* at 968, in turn quoting *Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1573 (Fed. Cir. 1997)). On the other hand, "'[t]he disclosure originally filed **does not . . . have to provide *in haec verba* support for the claimed subject matter at issue.**'" *Id.* (again quoting *Cordis Corp.*, 339 F.3d at 1364).

The Federal Circuit has explained:

> A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included [1] to convince a person of skill in the art that the inventor possessed the invention and [2] to enable such a person to make and use the invention without undue experimentation.

LizardTech, Inc. v. Earth resource Mapping, PTY, Inc., 424 F.3d 1336, 1345 (Fed. Cir. 2005) (internal citations omitted) (citing *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 997 (Fed. Cir. 2000); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed. Cir. 1995)); *see also Falko-Gunter Falkner*, 448 F.3d at 1366 (quoting this passage from *LizardTech*); *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006).

Applicants contend that the logic of the Office's position in view of the above standards, and particularly, the language describing the *Lilly* opinion appears to suffer from some internal contradictions as expressed in the above quote from the Action (not a direct quote from *Lilly)*. Applicant believe they have indeed described "one way" of performing the invention and identified the common characteristics of the claimed xylose isomerase as a minimum of identity for this given sequence along with a functional requirement (that the cell expressing this enzyme can convert xylose to xylulose). Therefore, the skilled artisan will understand that they have possession of the invention as claimed, thereby satisfying the Written Description requirement as defined in *Lilly* and the other (earlier and later) jurisprudence noted above.

Applicants also note that new claims 21 -24 (depending directly or indirectly from claim 1) increasingly raise the required sequence identity (to SEQ ID NO:1) of the claimed xylose isomerase to 80%, 90%, 95% and full identity, respectively. Claims of such narrower should present even less of an issue with respect to adequate description, even *in haec verba*, by the language of the specification.

Applicants also respectfully call the Examiner's attention to hypothetical Example 14 in the PTO's "Synopsis of Application of Written Description Guidelines available at http://www.uspto.gov/web/menu/written.pdf.

Compliance with the written description requirement is essentially a fact based inquiry that will necessarily vary depending on the nature of the invention claimed. The hypothetical examples of the Synopsis are considered to be helpful in understanding how to apply the relevant law (but do not create a rigid test). In this case, the facts are similar in nature to the hypothetical example, with some differences in the range of identity claimed. The claim in hypothetical "Example 14" is directed to variants that are at least 95% identical to the underlying sequence

and possess a particular function. In the hypothetical analysis, the specification disclosed only the underlying sequence but no variants at all. The present claims focuses on a "range" of variants that fall within the definition of being at least 70% identical to the underlying sequence (SEQ ID NO:1) and having the indicated function in the cell . Moreover, the specification provides a broader, yet more specific range in the paragraph bridging pages 7 and 8:

> A nucleotide sequence encoding the xylose isomerase may be selected from the group consisting of:
> (a) nucleotide sequences encoding a polypeptide comprising an amino acid sequence that has at least 40, 45, 49, 50, 53, 55, 60, 70, 80, 90, 95, 97, 98, or 99% sequence identity with the amino acid sequence of SEQ ID NO. 1…

The analysis in the above "Synopsis" concluded that adequate written description is present when:

> *There is actual reduction to practice of the single disclosed species.*
>
> **(analogous to the present disclosure of SEQ ID NO:1)**
>
> *The specification indicates that the genus of proteins that must be variants of SEQ ID NO:3 does not have substantial variation since all of the variants must possess the specified catalytic activity and must have at least 95% identity to the referenced sequence, SEQ ID NO:3.*
>
> **(the present disclosed range of variation specifically includes 70, 80, 90 and 95% identity, which are claimed in claim 1 and new claims 21-23; again, this is not intended to be a rigid test…)**
>
> *The single species disclosed is representative of the genus because all members have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity.*
>
> **The assay for the indicated xylose isomerase enzymatic activity is provided in Example I, and moreover, is well established in the art**
>
> *One of skill in the art would conclude that applicant was in possession of the necessary common attributes possessed by the members of the genus.*

Thus, in that hypothetical example, the disclosure meets the requirements of 35 U.S.C. 112, first paragraph, as providing adequate written description for the claimed invention when the genus ranged to 95% or more sequence identity. Applicants believe, as noted above, that their disclosure adequate describes the claimed invention when the recited identity is 70% or greater. *A fortiori*, this applies to sequence identities of at least 80, 90 and 95%. Taken literally, the hypothetical example clearly covers the "at least 95%" language of claim 23. However, since the determination is to be made on a case-by-case basis, Applicants respectfully submit that their

invention is adequately described for sequence identities of 70% or more. Applicants refer again to the post-filing evidence discussed above (that a protein with 83% identity works) and believe that it would be unfair, given the nature of their contribution to the art, to restrict them to, for example, 95% identity under § 112, first paragraph.

To the extent that the Office may have conflated the Written Description and the Enablement requirements of § 112, first paragraph, the earlier discussion of the latter should be considered in reconsidering this rejection. Applicants therefore believe that, in view of the amendments and foregoing remarks, the rejection of all amended and new claims based on the alleged lack of adequate written description may properly be withdrawn.

IV. Rejection Under 35 U.S.C. 103(a) (Claims 1-5)

Claims 1-5 were rejected under 35 U.S.C. 103(a) as being obvious over Guan *et al.* (*US Patent 5,643,758*; published 07/01/1997) (hereinafter "Guan") or Karlsson *et al.* (*Eur J Biochem.*, 2001, *268*:6498-6507) (hereinafter "Karlsson") in view of Accession Q9P8C9 (published 2000-10-01).

Guan ("entire patent") allegedly discloses expression vectors with promoters, prokaryotic host cells such as *E. coli* and eukaryotic host cells such as yeast, and methods for making, expressing, isolating, and purifying any-protein fused to the *E. coli* maltose binding protein (MBP) using such expression vectors and cells. Guan allegedly discloses that these methods and products are useful for purifying virtually any hybrid polypeptide molecule employing recombinant techniques.

Karlsson ("entire publication") allegedly discloses host cells of the filamentous fungus *Trichoderma reesei* transformed with an expression vector that encodes Ce161A(EG IV).

According to the Office, the teachings of Guan and Karlsson differ from the claims in that there is **no disclosure** of transformation of a yeast or filamentous fungus (such as *Trichoderma reesei*) host cell with a polynucleotide encoding a xylose isomerase which comprises an amino acid sequence at least 70% identical to SEQ ID NO:1.

The Office has cited Accession Q9P8C9[1] as disclosing a xylose isomerase protein, the amino acid sequence of which is, in fact, SEQ ID NO:1.

The Office concluded that it would have been obvious to transform yeast cells using the approach taught by Guan or *Trichoderma reesei* cells using the disclosure of Karlsson with the

[1] equivalent to GenBank Accession No. AJ249909, from a deposit by the following "authors": Harhangi,H.R., Akhmanova,A.S., Emmens,R., van der Drift,C., de Laat, W.T., van Dijken, J.P., Jetten, M.S., Pronk, J.T. and Op den Camp, H.J. This includes the four present inventors -- Op Den Camp. Harhangi, Van der Drift and Pronk).

polynuc1eotide encoding the xylose isomerase disclosed in Accession Q9P8C9 (the amino acid sequence of which is 100% identical to SEQ ID NO:1). One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order **to express and purify the xylose isomerase** taught by Accession Q9P8C9. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation for success because recombinant techniques for heterologous or homologous expression of proteins are well developed in the art. Thus, it was allegedly obvious and within the ordinary skill in the art to make and use the claimed invention as a whole, making it clearly *prima facie* obvious.

Applicants' Response

The legal test for obviousness was articulated by the Federal Circuit, *inter alia,* in *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988). The burden of establishing a case of *prima facie* obviousness rests with the Patent and Trademark Office. *Fine* at 1598.

It respectfully is submitted that a legally sufficient *prima facie* case of obviousness has not been adduced here because the cited art does not suggest the present compositions (transformed eukaryotic cells as claimed) nor do they provide a basis for a reasonable expectation of success in making and using such compositions. The cited prior art does not suggest to those of ordinary skill that they should make the claimed compositions. Moreover, the cited prior art as a matter of logic, do not reveal that the invention could have been practiced with a reasonable expectation of success. Absent a hindsight analysis of Applicants' disclosure (discussed further below), there is no guidance in the art itself as to how to combine the prior art references so as to achieve the result of the claims at issue.

A more precise discussion of the cited references is as follows. Guan deals with a prokaryotic or eukaryotic expression system that involves fusing a desired gene (*i.e.*, coding sequence) to be expressed to DNA encoding the maltose binding protein (MBP). This facilitates purification of the encoded fusion polypeptide on the basis of the presence of the MBP sequence.

Karlsson deals with the transformation of *Trichoderma reesei* cells with an *endogenous* cellulase gene and with expression (production) and purification of the cellulase enzyme.

The Examiner alleges that the skilled person would have combined Karlsson or Guan with the DNA sequence (SEQ ID NO:1) disclosed in Accession Q9P8C9. to arrive (presumably without any further conceptive or inventive effort) to the claimed invention. Applicants believe that the Office's combination of Guan or Karlsson with the disclosure of SEQ ID NO:1, is logically, technically and legally erroneous.

The Office Action clearly appears focused on recombinant **expression/purification** of xylose isomerase. It appears to Applicants that the Office's statement concerning the "reasonable expectation for success" refers to success in purifying xylose isomerase produced recombinantly in eukaryotic cells. However, that is not the purpose of the present invention, nor the subject matter that is being claimed. This makes the Guan reference all the more irrelevant – as it is a technical disclosure of an improved production method expressly designed to aid in purification of a desired protein by taking advantage of the MBP fusion protein "trick." The present claims do not involve production and purification of xylose isomerase, and cannot utilized this MBP method in any imaginable way. Moreover, Applicants do not allege that they have invented the concept of recombinantly expressing a protein in eukaryotic cells, and the claims are not so directed.

Karlsson discloses expression of an endogenous protein. It does not suggest, or provide a basis, for expressing in a eukaryotic cell, an exogenous DNA, let alone xylose isomerase-encoding DNA. The present invention, as presently claimed, solves the long-standing and difficult problem (see, for example, van Maris reference which the Office cited in the context of its enablement rejection) of introducing and successfully expressing in a eukaryotic cell, such as a yeast or fungal cell, DNA encoding xylose isomerase such that expression of this enzyme confers upon the cell the ability to convert directly, in a single step, xylose to xylulose. As discussed in the van Maris reference (*supra*), for example, the fact that those skilled in the art had not been able previously to accomplish this feat must be viewed as one indicium of non-obviousness.

Furthermore, a fair reading of Guan and Karlsson clearly indicates that neither reference would suggest to one skilled in the art to identify and use the DNA sequence SEQ ID NO:1 that encodes xylose isomerase (disclosed in Accession Q9P8C9), or a sequence that is at least 70% identical to it (or at least 80%, 90%, or 95% identical to it, as claimed in new claims 21-23) for the use claimed in claim 1. It is not surprising that Karlsson does not provide even the most meager suggestion to use the published nucleotide or amino acid sequence of xylose isomerase since this reference is preoccupied with expression of one particular endogenous (and unrelated) gene in one particular species *Trichoderma reesei*. It is also evident that Guan does not remotely suggest the use of the xylose isomerase sequence in accordance with the rejected claims since Guan is simply focused on a method for purifying recombinant proteins. It should be noted that the hypothetical, and seemingly random, combination of Guan with the published sequence of xylose isomerase DNA and protein (SEQ ID NO:1) would not lead the skilled person to the present invention since the invention does not employ the MBP technology.

The reasoning used by the Office can at best be viewed as hindsight reconstruction which has long been considered to be impermissible. See, for example, *In re Vogel* 150 USPQ 445,449 (1966 C.C.P.A.)("The rejection is based on an improper piecemeal reconstruction of the prior art made in light of appellant's disclosure and not taught or made obvious by the reference disclosures."); *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985) ("When prior art references require selective combination by the court to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself."). Here, the Office has used Applicants' disclosure and claims as guide to picking and choosing among the prior art references that are actually quite unrelated to one another (and the primary references are clearly irrelevant to the present invention) and haphazardly piecing those references together to fashion the present obviousness rejection which Applicants contend is improper.

For the reasons indicated above, and further in view of the amendments to the claims, Applicants believe that it would be proper to withdraw the above rejections under § 103(a) and respectfully requests the Office to do so.

IV. CONCLUSION

In conclusion, it is respectfully requested that the above amendments, remarks and requests be considered and entered. Applicants request that the currently presented claims, including amended and new claims, be allowed.

If the Examiner deems it helpful, he is requested to phone the undersigned at the phone number shown below to discuss the present amendments and response.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /Shmuel Livnat/
Shmuel Livnat
Registration No. 33,949

SL:jv

Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528

G:\BN\N\NEDE\Op Den Kamp=1 (NOB-8)\PTO\2007-09-11_Resp&Amd_OA1_OpDenCamp1 .DOC